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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/016,627	12/10/2001	Emil Wei-Ming Fu	4-31692A	4092

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CORPORATE INTELLECTUAL PROPERTY
ONE HEALTH PLAZA 104/3
EAST HANOVER, NJ 07936-1080

EXAMINER	
VENCI, DAVID J	

ART UNIT	PAPER NUMBER
1641	

DATE MAILED: 04/19/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/016,627	FU ET AL.	
	Examiner	Art Unit	
	David J. Venci	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *December 8, 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-49* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-49* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *December 8, 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Allowable Subject Matter

The indicated allowability of claims 1-49 is withdrawn in view of newly discovered teachings of Chait et al. (US 6,391,649). Rejections based on the newly cited reference follow.

Specification

The disclosure is objected to because of the following informalities:

> Throughout the specification, the recitation of the term "inverse" is indefinite because the scope of the definition of the term "inverse" is not clear. Applicants are required to provide a definition for the term "inverse", or provide correlation to an art-recognized definition.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-49 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The specific claim rejections under 35 USC 112, second paragraph, set forth infra, may be considered relevant to other claims not explicitly mentioned, as deemed reasonably appropriate.

In claim 1, step (a), the recitation of "equal protein pools" is indefinite because it is not clear how protein pools are "equal." It is not clear how a reference sample pool is "equal" to an experimental sample pool.

In claim 1, step (f), the recitation of "inverse labeling pattern" is indefinite because the scope of the definition of the term "inverse" is not clear in both Applicants' specification and Applicants' clarifying remarks. Applicants argue that the term "inverse labeling pattern" is broadly defined on page 11 of the specification meaning "a qualitative mass shift or an isotope peak intensity ratio reversal" (see Applicants' Reply at p. 4, second paragraph, lines 2-4) (emphasis added). However, Applicants also acknowledge that the term "inverse" has a more limited definition meaning "a reversal in the signal intensities" (see Applicants' Reply at sentence bridging pp. 4-5). Both Applicants' specification and Applicants' clarifying remarks do not appear to resolve how a "qualitative mass shift" amounts to the creation of an "inverse labeling pattern" or how the definition of the term "inverse," dictionary or otherwise, applies to the concept of a "qualitative mass shift."

In claim 23, step (b), the recitation of "during labeling" lacks antecedent basis. In addition, the recitation of "proteolyzing... with isotopically labeled water" is indefinite because it is not clear how water, by itself, is capable of proteolysis.

In claim 35, step (c), the recitation of "labeling each peptide pool with isotopically labeled water" is indefinite because it is not clear how water, by itself, is capable of labeling.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-12, 14, 16-19, 21-22 and 47-49 are rejected under 35 U.S.C. 102(e) as being anticipated by Chait et al. (US 6,391,649).

Chait et al. describe a method for identifying a differentially expressed protein in two different samples (see Abstract, "comparing the levels of cellular components, such as proteins, present in samples which differ in some respect from each other") comprising the steps of: providing two equal protein pools (see col. 11, lines 56-57, "high abundance proteins derived from two pools") from each of a reference sample (see col. 12, lines 11-12, "expressing population is designated 'CLN2+'") and an experimental sample (see col. 12, lines 12-13, "non-expressing population is designated 'cln2-'"), labeling the protein pools with a substantially chemically identical isotopically different protein labeling reagent for proteins, wherein one pool from each of the reference and experimental pools is labeled with an isotopically heavy protein labeling reagent to provide an isotopically heavy-labeled reference pool and an isotopically heavy-labeled experimental pool, and wherein the remaining reference and experimental pools are labeled with an isotopically light protein labeling reagent to provide an isotopically light-labeled reference pool and an isotopically light-labeled experimental pool (see col. 12, lines 14-18), combining the isotopically light labeled reference pool with the isotopically heavy-labeled experimental pool to provide a first protein

mixture (see col. 12, lines 16-18, "A second combined sample contained 1 mL of unlabeled (^{14}N) extract of $CLN2^{+}$ plus 1 mL of ^{15}N-labeled extract of $clin2^{-}$"), combining the isotopically heavy-labeled reference pool with the isotopically light-labeled experimental pool to provide a second protein mixture (see col. 12, lines 14-16, "A first combined sample contained 1 mL of unlabeled (^{14}N) extract of $cln2^{-}$ plus 1 mL of ^{15}N-labeled extract of $CLN2^{+}$"), detecting the labeled proteins from each of the two mixtures (see col. 13, lines 14-15, "Mass spectrum measurements were obtained"), comparing the labeling pattern (see col. 14, lines 1-3, "comparing the sum of the intensities of the isotopically resolved components of the unlabeled peptide with the corresponding sum from the ^{15}N peptide"), wherein an inverse labeling pattern is indicative of the differentially expressed protein (see Table IV).

With respect to claims 2, 14 and 28, Chait et al. describe a method further comprising the step of enzymatically or chemically cleaving the labeled proteins (see col. 12, line 67, "trypsin solution").

With respect to claims 3-6 and 11-12, Chait et al. describe a method further comprising the step of detecting and sequencing the peptides with MS/MS (see col. 15, lines 38-41).

With respect to claims 7-10 and 15, Chait et al. describe a method further comprising the step of separating the labeled proteins with RP-HPLC (see col, 12, lines 26-28).

With respect to claims 14, Chait et al. describe a method further comprising the step of subjecting the samples to at least one fractionation technique (see col. 17, line 12, "pelleted, washed").

With respect to claims 17-19, Chait et al. describe a method wherein the proteins are labeled with ^{18}O isotope (see col. 5, line 55).

With respect to claims 49, Chait et al. describe a method wherein the assimilable source is an ammonium salt (see col. 9, line 65).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 23-28, 30, 32-40, 42 and 44-46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schnolzer et al., 17 ELECTROPHORESIS 945 (1996) in view of Chait et al. (US 6,391,649).

Schnolzer et al. teach a method of identifying proteins in a sample comprising the steps of: providing two equal protein pools (see p. 950, col. 2, first full paragraph, line 2), proteolyzing each protein pool with isotopically labeled water (see p. 950, col. 2, first full paragraph, line 3), combining the protein pools (see p. 950, col. 2, first full paragraph, line 2), detecting the labeled peptides (see p. 950, col. 2, first full paragraph, lines 15-17), and comparing the labeling pattern (see p. 950, col. 2, first full paragraph, lines 6-8).

Schnolzer et al. do not teach a method for identifying differentially expressed protein in two different protein samples.

However, Chait et al. describe a method for identifying a differentially expressed protein in two different samples (see Abstract, "comparing the levels of cellular components, such as proteins, present in samples which differ in some respect from each other") comprising the steps of: providing two equal

protein pools (see col. 11, lines 56-57, "high abundance proteins derived from two pools") from each of a reference sample (see col. 12, lines 11-12, "expressing population is designated 'CLN2+'") and an experimental sample (see col. 12, lines 12-13, "non-expressing population is designated 'cln2-'"), labeling the protein pools with a substantially chemically identical isotopically different protein labeling reagent for proteins, wherein one pool from each of the reference and experimental pools is labeled with an isotopically heavy protein labeling reagent to provide an isotopically heavy-labeled reference pool and an isotopically heavy-labeled experimental pool, and wherein the remaining reference and experimental pools are labeled with an isotopically light protein labeling reagent to provide an isotopically light-labeled reference pool and an isotopically light-labeled experimental pool (see col. 12, lines 14-18), combining the isotopically light labeled reference pool with the isotopically heavy-labeled experimental pool to provide a first protein mixture (see col. 12, lines 16-18, "A second combined sample contained 1 mL of unlabeled (^{14}N) extract of $CLN2^{+}$ plus 1 mL of ^{15}N-labeled extract of $clin2^{-}$"), combining the isotopically heavy-labeled reference pool with the isotopically light-labeled experimental pool to provide a second protein mixture (see col. 12, lines 14-16, "A first combined sample contained 1 mL of unlabeled (^{14}N) extract of $cln2^{-}$ plus 1 mL of ^{15}N-labeled extract of $CLN2^{+}$"), detecting the labeled proteins from each of the two mixtures (see col. 13, lines 14-15, "Mass spectrum measurements were obtained"), comparing the labeling pattern (see col. 14, lines 1-3, "comparing the sum of the intensities of the isotopically resolved components of the unlabeled peptide with the corresponding sum from the ^{15}N peptide"), wherein an inverse labeling pattern is indicative of the differentially expressed protein (see Table IV).

Therefore, it would have been obvious for a person of ordinary skill in the art to perform the method of identifying proteins in a sample, as taught by Schnolzer et al., to identifying differentially expressed protein in two different protein samples because Chait et al. discovered a method for analyzing post-translational modifications (see col. 4, lines 11-14) to analyze the effects of environmental stimuli (e.g. drugs, hormones, etc.) in two or more biological samples (see col. 3, lines 47-60) in order to gain insight into mechanisms of drug action, viral infection, etc. (see col. 1, lines 28-54). In addition, Chait et al.

discovered a method to ensure that any change in isotopic ratios is not caused by the isotopic enrichment itself (see col. 8, lines 61-64).

With respect to claim 35, step (c), Schnolzer et al. teach a method wherein "peptide products continue to interact with these proteases and undergo repeated binding/hydrolysis cycles, resulting in complete equilibrium of both oxygens in the carboxy terminus of the fragment with oxygen from solvent water" (see Abstract).

Claims 13, 15 and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Aebersold et al. (US 6,670,194) in view of Chait et al. (US 6,391,649).

Aebersold et al. teach a method of identifying proteins in a sample comprising the steps of: providing two equal protein pools (see col. 5, lines 61-66), labeling each protein pool with a isotopically different labeling reagent (see col. 5, lines 61-66), combining the protein pools (see col. 6, lines 2-3), detecting the labeled peptides (see col. 6, line 9), and comparing the labeling pattern (see col. 6, lines 13). With respect to claims 13 and 15, Aebersold et al. teach an affinity chromatographic fractionation of proteins (see e.g. col. 17, line 49, "panning") prior to step (a). With respect to claim 20, Aebersold et al. describe a labeling reagent containing an affinity tag (see Abstract).

Aebersold et al. do not provide two protein pools from each of a reference and an experimental sample.

However, Chait et al. describe a method for identifying a differentially expressed protein in two different samples (see Abstract, "comparing the levels of cellular components, such as proteins, present in samples which differ in some respect from each other") comprising the steps of: providing two equal protein pools (see col. 11, lines 56-57, "high abundance proteins derived from two pools") from each of a

reference sample (see col. 12, lines 11-12, "expressing population is designated 'CLN2+'") and an experimental sample (see col. 12, lines 12-13, "non-expressing population is designated 'cln2-'"), labeling the protein pools with a substantially chemically identical isotopically different protein labeling reagent for proteins, wherein one pool from each of the reference and experimental pools is labeled with an isotopically heavy protein labeling reagent to provide an isotopically heavy-labeled reference pool and an isotopically heavy-labeled experimental pool, and wherein the remaining reference and experimental pools are labeled with an isotopically light protein labeling reagent to provide an isotopically light-labeled reference pool and an isotopically light-labeled experimental pool (see col. 12, lines 14-18), combining the isotopically light labeled reference pool with the isotopically heavy-labeled experimental pool to provide a first protein mixture (see col. 12, lines 16-18, "A second combined sample contained 1 mL of unlabeled (^{14}N) extract of $CLN2^+$ plus 1 mL of ^{15}N-labeled extract of $clin2^-$"), combining the isotopically heavy-labeled reference pool with the isotopically light-labeled experimental pool to provide a second protein mixture (see col. 12, lines 14-16, "A first combined sample contained 1 mL of unlabeled (^{14}N) extract of $cln2^-$ plus 1 mL of ^{15}N-labeled extract of $CLN2^+$"), detecting the labeled proteins from each of the two mixtures (see col. 13, lines 14-15, "Mass spectrum measurements were obtained"), comparing the labeling pattern (see col. 14, lines 1-3, "comparing the sum of the intensities of the isotopically resolved components of the unlabeled peptide with the corresponding sum from the ^{15}N peptide"), wherein an inverse labeling pattern is indicative of the differentially expressed protein (see Table IV).

Therefore, it would have been obvious for a person of ordinary skill in the art to perform the method of identifying proteins in a sample, as taught by Aebersold et al., by providing two protein pools from each of a reference and an experimental sample because Chait et al. discovered that differentially expressed proteins can be analyzed for post-translational modifications (see col. 4, lines 11-14) to analyze the effects of environmental stimuli (e.g. drugs, hormones, etc.) on two or more biological samples (see col. 3, lines 47-60) in order to gain insight into mechanisms of drug action, viral infection, etc. (see col. 1, lines 28-54). In addition, Chait et al. discovered a method to ensure that any change in isotopic ratios is not caused by the isotopic enrichment itself (see col. 8, lines 61-64).

Claims 29 and 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schnolzer et al., 17 ELECTROPHORESIS 945 (1996) and Chait et al. (US 6,391,649) as applied to claim 23, and further in view of Aebersold et al. (US 6,670,194).

Schnolzer et al. and Chait et al. describe a method for identifying a differentially expressed protein as substantially described supra. The aforementioned references do not teach a fractionation step prior to step (a).

However, Aebersold et al. teach an affinity chromatographic fractionation of proteins (see e.g. col. 17, line 49, "panning") prior to step (a) as a preparative step in the analysis of membrane proteins (see col. 17, line 28). Therefore, it would have been obvious for a person of ordinary skill in the art to practice the method of identifying differentially expressed proteins, as taught by Schnolzer et al. and Chait et al., with a fractionation step prior to step (a) because Aebersold et al. discovered that panning and labeling membrane proteins with isotopic affinity tags can be used to identify important diagnostic or therapeutic targets (see col. 17, lines 49-52) without the step of solubilizing membrane proteins prior to analysis, thus avoiding a major complication facing prior art methods which require solubilization of membrane proteins prior to analysis.

Claims 41 and 43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schnolzer et al., 17 ELECTROPHORESIS 945 (1996) and Chait et al. (US 6,391,649) as applied to claim 35, and further in view of Aebersold et al. (US 6,670,194).

Schnolzer et al. and Chait et al. describe a method for identifying a differentially expressed protein as substantially described supra. The aforementioned references do not teach a fractionation step prior to step (a).

However, Aebersold et al. teach an affinity chromatographic fractionation of proteins (see e.g. col. 17, line 49, "panning") prior to step (a) as a preparative step in the analysis of membrane proteins (see col. 17, line 28). Therefore, it would have been obvious for a person of ordinary skill in the art to practice the method of identifying differentially expressed proteins, as taught by Schnolzer et al. and Chait et al., with a fractionation step prior to step (a) because Aebersold et al. discovered that panning and labeling membrane proteins with isotopic affinity tags can be used to identify important diagnostic or therapeutic targets (see col. 17, lines 49-52) without the step of solubilizing membrane proteins prior to analysis, thus avoiding a major complication facing prior art methods which require solubilization of membrane proteins prior to analysis.

Response to Arguments

In prior Office Action, Examiner objected to the disclosure for the recitation of "differentially expressed." Applicants' clarifying remarks in the Reply filed December 8, 2004, are fully persuasive. Accordingly, this objection is withdrawn.

In prior Office Action, Examiner objected to the disclosure for the apparent interchangeable usage of the terms "inverse", "reversal", "converse", and "inverted." Applicants' clarifying remarks in the Reply filed December 8, 2004, appear to correlate the definition of the terms "reversal", "converse", and "inverted" with the definition of the term "inverse," i.e. the terms "inverse", "reversal", "converse", and "inverted" have identical definitions. The objection to the terms "reversal", "converse", and "inverted" is withdrawn

inasmuch as the terms "reversal", "converse", and "inverted" have the same definition as the term "inverse."

With respect to Applicants' clarifying remarks pertaining to the definition of the term "inverse," Applicants' remarks have been carefully considered but are not persuasive because the scope of the definition of the term "inverse" is not clear in both Applicants' specification and Applicants' clarifying remarks. Applicants acknowledge that the term "inverse labeling pattern" is broadly defined on page 11 of the specification meaning "a qualitative mass shift or an isotope peak intensity ratio reversal" (see Applicants' Reply at p. 4, second paragraph, lines 2-4) (emphasis added). However, Applicants also acknowledge that the term "inverse" has a more limited definition meaning "a reversal in the signal intensities" (see Applicants' Reply at sentence bridging pp. 4-5). Both Applicants' specification and Applicants' clarifying remarks do not appear to resolve the scope of the definition of the term "inverse" by describing how a "qualitative mass shift" amounts to the creation of an "inverse labeling pattern" or how the definition of the term "inverse," dictionary or otherwise, applies to the concept of a "qualitative mass shift."

In prior Office Action, claims 1-49 were provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 1-49 of copending Application No. 10/412,964. Applicants have cancelled claims 1-49 of copending Application No. 10/412,964. Accordingly, this rejection is withdrawn.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Venci whose telephone number is 571-272-2879. The examiner can normally be reached on 08:00 - 16:30 (EST). If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached on 571-272-0823. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

David J Venci
Examiner
Art Unit 1641

djv

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04/11/05